REMARKS

The Office Action dated September 27, 2007 has been carefully reviewed and the foregoing amendments are made in response thereto. In view of the above amendments and following remarks, Applicants respectfully request reconsideration of this application and timely allowance of the pending claims.

By this paper, independent claims 53 and 66 have been rephrased to clarify the feature that the first polymerizable mixture comprises first cells. Similarly, claim 56, which depends from claim 53, has been amended to clarify that the second polymerizable mixture comprises second cells; while claim 70, which depends from claim 66, has been amended to clarify that the second polymerizable mixture comprises second cells and the third polymerizable mixture comprises third cells. The above-mentioned amendments merely rephrase the claim language to clarify the features that had been previously recited, thus no prohibited new matter is introduced to the original disclosure. Furthermore, independent claims 53 and 66 have been amended to recite that a volume of the first polymerizable mixture is placed in an osteochondral tissue space and the first polymerizable mixture is in direct contact with the osteochondral tissue underneath. Support for these amendments can be found at least in paragraphs [0012] on page 5, [0022] on page 7, [00158] on page 48, [00165] on page 50, [00197] on page 64, and FIG. 2. Moreover, claims 71 and 73, previously dependent on claim 66, have been amended to be dependent on claim 70. In view of the amended claim 56, claim 87 has been cancelled to avoid redundancy. Thus, no prohibited new matter is introduced to the original disclosure.

Upon entry of this amendment, claims 53 to 78 will be pending.

Summary of the Office Action of September 27, 2007

1. Claims 53, and 61 to 63 are rejected under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Patent No. 6,949,252 to Mizuno et al. (hereinafter "Mizuno et al.").

2. Claims 54 to 60, 64 to 78, and 87 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Mizuno et al. further in view of U.S. Patent Application Publication No. 2003/0077821 to Sah et al. (hereinafter "Sah et al."), U.S. Patent No. 6,244,893 to Langer et al.

(hereinafter "Langer et al."), and Anseth et al., Journal of Controlled Release, 2002 (hereinafter "Anseth et al.").

Claim Rejections under 35 U.S.C. § 102(e)

Claims 53 and 61 to 63 are rejected under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Patent No. 6,949,252 to Mizuno et al. (hereinafter "Mizuno et al.").

Applicants respectfully disagree with the Examiner for the reasons set forth below.

It is axiomatic that a claim is anticipated only if each and every element as set forth in the claim is disclosed in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Claim 53 has been amended to recite that a volume of the first polymerizable mixture is placed in an osteochondral tissue space and the first polymerizable mixture is in direct contact with the osteochondral tissue underneath. Claim 53 has also been rephrased to clarify that the first polymerizable mixture comprises first cells.

Applicants respectfully submit that Mizuno et al. do not anticipate amended claim 53 and its dependent claims because unlike the claimed method, the cell-seeded layer of Mizuno et al. is not in direct contact with the osteochondral tissue of the recipient.

Mizuno et al. relates to specific types of compositions and methods for preparing tissues or tissue constructs that include an integration layer and a cellular matrix seeded with living cells. Specifically, Mizuno et al. disclose that the integration layer is in direct contact with an organ or tissue and is an interface between a later-applied cell-seeded support matrix and the native tissue or organ. (See column 12, lines 12-20) Thus, in the Mizuno composition, the integration layer is the first layer and in direct contact with an tissue, while the cell-seeded support matrix is the second layer and is insulated from other cells by the integration layer.

Mizuno et al. specifically teach that when a multi-layered tissue construct is implanted into an articulating joint or bone tissue place, i.e., osteochondral tissue place, the first layer not only contains no cells, but also prevents the infiltration of cells from underlying bone tissue into the second layer. (See column 25, claim 1; column 13, lines 38-53; and column 12, lines 31-37) Citing the disclosure at column 23, lines 20-25, the Examiner asserts that Mizuno et al. disclose a cell-seeded layer in direct contact with the tissue underneath. It is true that Mizuno et al. suggest that when used in a skin tissue space, an integration layer may further contain appropriate nutrient materials capable of producing a tissue replica of the dermis, wherein the nutrient materials can be fibroblast cells. (See column 23, lines 20-25) However, this supposed cell-seeded integration layer is placed only in a skin tissue place, not in a osteochondral tissue place. Thus, Mizuno et al. do not disclose or suggest that a cell-seeded first polymerizable mixture be placed in an osteochondral tissue place, let alone be in directed contact with the osteochondral tissue underneath, as the presently amended method claims.

Since Mizuno et al. fail to disclose an essential element of the claimed invention, claim 53 is not anticipated by Mizuno et al. Similarly, claims 61 to 63 are not anticipated by Mizuno et al. because claims 61 to 63 are dependent from independent claim 53 and thereby include all the limitations of claim 53.

In view of the foregoing, Applicants respectfully request that the rejections to claims 53 and 61 to 63 under 35 U.S.C. § 102(e) be withdrawn.

Claim Rejections under 35 U.S.C. § 103(a)

Claims 54 to 60, 64 to 78, and 87 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Mizuno et al. further in view of U.S. Patent Application Publication No. 2003/0077821 to Sah et al. (hereinafter "Sah et al."), U.S. Patent No. 6,244,893 to Langer et al. (hereinafter "Langer et al."), and Anseth et al., Journal of Controlled Release, 2002 (hereinafter "Anseth et al."). Specifically, the Examiner alleges that one of ordinary skill in the art would have been motivated to include a photopolymerizable polymer of Langer et al. and a photoinitiator of Anseth et al. in the methods of Mizuno et al. and Sah et al. to arrive at the present invention.

Applicants respectfully disagree with the Examiner for the reasons set forth below.

Establishing *prima facie* obviousness requires a showing that there are some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Recently, the United States Supreme Court also expressed the need to an "explicit" showing of "some apparent reason to combine the known elements in the fashion claimed by the patent at issue". *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. __, 127 S.Ct. 1727, slip op. at 14 (2007).

Applicants respectfully submit that the obviousness rejection fails because there is no suggestion available in the cited references or otherwise of record which would motivate one skilled in the art to combine or modify the prior art methods in such a way to arrive at the claimed method, as amended.

Claims 53 and 66 have been amended to recite that a volume of the first polymerizable mixture is placed in an osteochondral tissue space and the first polymerizable mixture is in direct contact with the osteochondral tissue.. Since claims 54 to 60 and 64 and 65 are directly or indirectly dependent from independent claim 53, they include all the limitations of claim 53. Similarly, claims 67 to 78 are directly or indirectly dependent from independent claim 66, and thereby include all the limitations of claim 66. Claim 87 has been canceled without prejudice.

Mizuno et al. not only fail to disclose a method wherein the cell-seeded layer is in direct contact with osteochondral tissue underneath, but teach away from such a method. It is true that Mizuno et al. contemplate placing a fibrolasts-seeded integration layer to a skin tissue place, but Mizuno et al. also state that depending upon the tissue into which the multi-layered composition will be incorporated, the integration layer, i.e., the first layer, may provide different functions. (Column 12, lines 21-24) Furthermore, in the circumstances where the multi-layered composition is applied to an osteochondral tissue place, Mizuno et al. emphasize that the layer in direct contact with the osteochondral tissue does not contain any cells and even prevents infiltration of cells from the bone tissue underneath. For example, Mizuno et al. state:

> "In one embodiment, the integration layer prevents the infiltration of blood vessels and unwanted cells from underlying bone tissue into a chondrocyte seeded matrix implanted into an articulating joint of a host." (Column 12, lines 32-37, underline added)

Claim 1 of Mizuno et al. also recites that:

> "...an implantable multilayered construct comprising: (i) a first integration layer that is, upon implantation, contacted with a joint lesion in situ and prevents infiltration of blood vessels and cells from underlying bone tissue into an implanted cellular support layer...". (Column 25, claim 1, underline added)

Thus, when the Mizuno composition is applied to a bone tissue place, the integration layer needs to shield the cell-seeded second layer from other cells, let alone contains any cells in itself. Below is another embodiment wherein the Mizuno composition is placed in a bone tissue place:

> "In a preferred embodiment, the protective layer comprises a proprietary solution, designated CT3, … a surgeon applies this aerosolized CT3 to subchondral bone in situ. In placing the cellular support layer, a surgeon places the polymer material in the lesion and, without waiting for it to fully polymerize, places the neo-cartilage into position. In this way, the layer facing subchondral bone seals-off the subchondral bone and holds the cellular support layer (e.g. neo-cartilage) in place. The outer protective layer … is applied in such a manner as to keep it below the articulating surface of the joint to prevent it from being displaced by friction." (Column 13, lines 38-53, underline added)

The protective layer described above serves as the first layer and is in direct contact with the subchondral bone tissue. The above process clearly indicates that the protective layer, i.e., the first layer, does not contain any cells and insulates the cell-seeded second layer from the subchondral bone tissue. In view of the foregoing, Mizuno et al. repeatedly teach that the cell-seeded layer of a multi-layered tissue construct is not in direct contact with osteochondral tissue.

Langer et al. disclose compositions for tissue engineering using photocrosslinkable polymeric hydrogels, and Anseth et al. investigate photoinitiated polymerizations in tissue engineering. However, Langer et al. only pertain to mono-layer tissue construct, while Anseth et al. focus on polymeric material, not method or process for fabricating tissue constructs. Neither Langer et al. nor Anseth et al. remotely suggest a method of producing a multi-layered tissue construct. One skilled in the art would not be motivated to apply the methods of Langer et al. and Anseth et al. to the Mizuno et al. method to make a composition wherein the cell-seeded layer is in direct contact with osteochondral tissue since such a method is repeatedly taught away by Mizuno et al.

Sah et al. is directed to a cultured, stratified cartilage tissue construct comprised of two or more cell-seeded cartilage layers and a method of making the cartilage tissue construct. It is important to note that Sah et al. fabricate the whole tissue construct in a culture medium outside of a living body, i.e., *in vitro*, and then implant the fabricated tissue construct into a tissue defect. In contrast, the claimed method produce a multi-layered tissue construct *in vivo*. It is common knowledge in the art that *in vivo* operations are much more stringent and restrictive than the *in* *vitro* operations due to safety concerns. Thus, one skilled in the art would not be motivated to apply the *in vitro* method of Sah et al. to the *in vivo* method of Mizuno et al.

In view of the foregoing, one skilled in the art would not be motivated to combine the methods disclosed by the cited references in the fashion claimed by the present application. Therefore, Applicants respectfully request that the rejections under 35 U.S.C. § 103 be withdrawn.

Conclusions

In view of the foregoing, it is believed that each ground of rejections set forth in the Office Action has been overcome. Thus, favorable reconsideration and allowance is respectfully solicited.

Except for issues payable under 37 C.F.R. 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a constructive petition for extension of time in accordance with 37 C.F.R. 1.136(a)(3).

Should the Examiner have any remaining questions, she is invited to telephone the undersigned.

Dated: January 23, 2008

Respectfully submitted,
COOLEY GODWARD KRONISH LLP

Cooley Godward Kronish LLP
ATTN: Patent Group
777 6th Street NW, Suite 1100
Washington, DC 20001
Tel: (202) 842-7861
Fax: (202) 842-7899

By:

Yong Lu
Reg. No. 56,038